Revision of EPA 1-liners pertaining to the EPA Memorandum (2/17/89) was performed (3/17/87 M. Silva.

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CHLOROBENZILATE

SB 950-105, Tolerance # 109

March 27, 1987

I. DATA GAP STATUS

Combined rat: Data gap, inadequate study, possible adverse effect indicated

Chronic rat: Data gap, inadequate study, possible adverse effect indicated

Chronic dog: Data gap, inadequate study, possible adverse effect indicated

Onco rat: Data gap, inadequate study, possible adverse effect indicated

Onco mouse: Data gap, inadequate study, possible adverse effect indicated

Repro rat: No data gap, no adverse effect

Terato rat: Data gap, inadequate study, no adverse effect indicated

Terato rabbit: Data gap, inadequate study, no adverse effect indicated

Gene mutation: Data gap, inadequate study, no adverse effect indicated

Chromosome: Data gap, no study on file.

DNA damage: Data gap, inadequate study, no adverse effect indicated

Neurotox: Not required at this time

----------**Note, Toxicolo**

one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name SB105CHL.CNA

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED

RAT

011 036843 Woodard Research Corp., 9/30/66. Entitled: "Chlorobenzilate: Safety evaluat by dietary feeding to rats for 104 weeks". Chlorobenzilate: 25% WP. 0, 40, 125, and 400 in diets of 30 rats/sex/group. Apparent NOEL = 40 ppm (tenuous evidence of focal testicul tubular degeneration effect: incidence of 0, 1, 3, and 3, in increasing dose groups). No acceptable, not upgradeable. Possible adverse effect indicated (testicular tubular degeneration), however value of study for risk assessment is limited due to study weakness Incorrect test article (not tech), no analysis of test article, dose levels not justified, insufficient animals, no clinical chemistry. J. Remsen (Gee), 12/3/85, (review not on dis
EPA 1-liner: Core Minimum, 2/17/89.

004 022796 Apparent reference to 011:036843, above.

CHRONIC

RAT

006 932658 Summary in Pesticides Toxicology 3:(9) 752-756 (1955) [Tab # 22 in vol.]. Entitled "Toxicology of Chlorobenzilate", [section on chronic feeding]. Chlorobenzilate, otherwise specified). 0, 50, and 500 ppm in diet. 20/group, except no female 50 ppm grou Possible adverse effect: dose-related increase in small and/or soft testes at 50 and 500 p No difference noted between groups in appearance of testes sections, and findings attribut investigators to normal ageing. **Not acceptable, not upgradeable**. No further information

requested from this report. An acceptable rat chronic or combined chronic/oncogenicity st is required. J. Remsen (Gee), 4/16/85, (review not on disk).
EPA 1-liner: Core Supplemental, 2/17/89.

010 36830-36832, 36834-36839, 36938 A series of interim reports and summary-form final reports on two limited-scale chronic studies, one of which was published and reviewed as 0 932658, above. Neither study nor combination satisfies the chronic testing requirement. information was presented in these brief reports which appears to need further examination (Summary report worksheet completed by J. Remsen (Gee), 12/3/85, (review not on disk).

004 022797 Brief RPAR rebuttal (Ciba-Geigy, 8/27/76) ref 006:932658, above.

DOG

The dog chronic study on the wettable powder, 011 036844, indicates "possible signif adverse effects", as noted in the one-liner, below (J. Remsen review, 12/4/85). The study flawed in several respects, so that meaningfulness of apparent responses cannot be very effectively assessed. Serious effects were observed only at a very high dose (3000 to 500 ppm). A repeat chronic study is required.

011 036844 Hazleton Labs, 8/6/65. Entitled "Two year dietary feeding study - purebred beagles: Chlorobenzilate". 25% WP ; 0, 100, 500, and 5000 (adjusted at week 20 to 3000) p Apparent NOEL = 500 ppm (anemia, extramedullary hematopoiesis in liver and spleen, erythro hyperplasia in bone marrow, marked weight loss, testicular atrophy, and other signs; particularly manifest at 5000 ppm level, with some of these signs at 3000 ppm level). **Not acceptable, not complete, not upgradeable** (too few dogs/group, inappropriate test article rather than tech), too few tissues examined (particularly an issue in mid-dose group, whic should have been carefully examined in view of possible significant toxicity in high dose group), no analysis of dosing solutions). J. Remsen (Gee), 12/4/85, (review not on disk).

EPA 1-liner: Core Minimum, 2/17/89.

004 932664 1-paragraph summary of 011:036844, above.

ONCOGENICITY

RAT

The rat 1978 NCI study would require a substantial amount of additional information t upgraded to an acceptable oncogenicity study. A chronic rat study is needed in any case, this study did not find a NOEL for non-neoplastic findings. An acceptable combined chronic/oncogenicity study could address the concern about adrenal cortical adenomas indic in the NCI study, as well as establish a NOEL for chronic effects. Medical Toxicology Ris Assessment Group may need additional data in the interim. **Even if the registrant does not elect to seek an upgrade of this study to acceptable status for an oncogenicity study, individual and summary data for testicular atrophy should be submitted.**

011 036846 NCI study conducted at Hazleton Labs (Vienna, VA), Report No. NCI-CG-TR-75, Entitled: "Bioassay of chlorobenzilate for possible carcinogenicity". [Same report as simultaneous mouse study, 11:36845]. Chlorobenzilate technical from Geigy Agricultural Chemicals (not further characterized). Dosages in diets of Osborne-Mendel rats: male: 0, and 3200 ppm initially, with high dose group treated continuously for 57 weeks, then taken treatment for 1 week every 5th week through week 78, finally 32 weeks off treatment prior term (week 111). Low-dose levels constant through week 79, then off treatment until term. Females: 0, 1175, and 2350 ppm initially. High dose off treatment at week 62 and every fi week through week 78, then off treatment through term. Low-dose group treated 78 weeks, t off treatment to term. Results: Appreciable weight decrements in high dose females and d related decrements in low- and high-dose males. Survival not affected. No NOEL indicated Behavioral effects indicated increased frequency of abdominal urine stains and hunched appearance in treated groups (no data provided). Apparent compound-related testicular atr

(p. 23). Possible oncogenic response: slight increases in adrenal cortical adenomas in bo sexes: statistical significance in low dose males and high dose females. **Not complete, no acceptable,** but useful data. Report lacks individual animal data, lacks quantitative summ and individual clinical observations data, lacks proper test article identification (batch whether commercial run technical, etc.), lacks documentation of dose levels administered a stability data of material in feed. Reviews by J. Remsen [Gee], 4/16/85, 12/3/85, (review on disk).

EPA 1-liner: Core Supplemental (for both rat and mouse), 2/17/89.

007 932670 Near-duplicate of the more complete report above, 011:036846.

MOUSE

011 036845 NCI study conducted at Hazleton Labs (Vienna, VA), Report No. NCI-CG-TR-75, Entitled: "Bioassay of chlorobenzilate for possible carcinogenicity". [Same report as simultaneous rat study, 11:36846] Chlorobenzilate technical from Geigy Agricultural Chemi (not further characterized). Dosages in diets of B6C3F1 mice: male: 0, 6000, and 12000 pp initially. Dosages were adjusted at week 9 to 0, 4000, and 8000 ppm. The low-dose group taken off treatment after week 78. High dose males were taken off the 8000 ppm diet after 52, and for 1 week every 5 weeks through week 78, and finally 12 weeks off treatment prior term (week 90). Adjusted low-dose levels of 4000 ppm remained constant through week 78, t males went off treatment until term. Females: 0, 3200, and 6400 ppm initially. High dose treatment at week 52 and every fifth week through week 78, then off treatment through term Low-dose group treated 78 weeks, then off treatment to term. Results: Body weight decrem in both sexes appeared dose-related. Hunched appearance was reported in treated groups (n data provided). No positive treatment effects on survival. More high-dose males survived week 60 than either of the other groups, hence possibility of bias in tumor incidence if n survival-adjusted. **Possible adverse effect:** Increased incidence of hepatocellular carcin in males and females, significant at all doses and not dose-related in dosage range studie

Not complete, not acceptable, but useful data. Report lacks individual animal data, lacks quantitative summary and individual clinical observations data, lacks proper test article identification (batch #, whether commercial run technical, etc.), lacks documentation of d levels administered and stability data of material in feed. Original review by J. Remsen [Gee], 4/16/85, 12/3/85, (review not on disk).
EPA 1-liner: Core Supplemental (for both rat and mouse), 2/17/89.

007 038486 Partial duplicate of above report (11:36845).

005 932669 Bionetics Research Labs and NCI, publ. in J. Nat. Cancer Inst. 42:1101-1114, 1969. Entitled "Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note". Chlorobenzilate, not characterized. Dosage 215 mg/kg by gavage (first 4 weeks), 603 ppm in diet (balance of treatment period) to 18 mice/sex/strain (two strains). **Possible adverse effects:** ("hepatomas" in males only, both strains). **Not acceptable, not upgradeable**: Too few animals/group, only one treatment grou hence insufficient statistical power for meaningful evaluation. No further information required of this study, however a valid mouse study is required. J. Remsen (Gee), 4/16/85 (review not on disk).
EPA 1-liner: study not acceptable, 2/17/89.

004 932665 (Commentary from Ciba-Geigy in rebuttal to an EPA RPAR document. Rebuttal d 8/27/76. Section entitled "18-month mouse study, Bionetics, 1969 (Appendix 35)"; pp. 50-5 Commentary questions value of study 005:932669, above, indicating many flaws of the study.

REPRODUCTION

RAT

Note that the acceptable reproduction study below, 012/014:036847-036849, originally indicated a "possible significant adverse effect", based on bone marrow hypoplasia in high

(1000 ppm) adult F_1 females. The investigators judged the finding to be a treatment respo
(stamped page 151). The original 1985 CDFA review indicated that this study represented a "significant adverse effect" [based exclusively on parental toxicity]. In the present case degree of effect was minor and the effect was seen only at a high dose. A degree of paren toxicity is normally **expected** in the highest dosage group to demonstrate adequacy of dosa levels. For this reason, the evaluation of this study is amended to remove the "significa adverse effects" flag.

**** 012/014:36847-36849 Toxicogenics, Inc., 3/24/82. Entitled: "Two-generation reproducti study in albino rats with chlorobenzilate technical" (Study 450-0277). Chlorobenzilate, t (94.9%). 0, 15, 300, and 1000 ppm in diet. Reproductive effects NOEL = HDT = 1000 ppm (n effects). Parental toxicity NOEL = 300 ppm (bone marrow hypoplasia in high dose (1000 ppm adult F_1 females). Study acceptable. J. Remsen (Gee), 12/4/85, (review not on disk).

002 932671 Woodard Research Corp., [pre- 8/27/65]. Entitled "Chlorobenzilate: Three- generation reproduction study in the rat". Chlorobenzilate 25W [wettable powder], 0, 25 a ppm in diet. No adverse effects indicated. **Not acceptable, not upgradeable:** Technical material not tested, no rationale for dosages employed and no evidence that dosages approa a toxic level, no dietary analysis. NOEL cannot be determined. No adverse effects indica No further information needed from this report. J. Remsen (Gee), 4/15/85, (review not on disk).
EPA 1-liner: Study not acceptable, 2/17/89.

015 036850 Duplicate of 002:932671, above.

004 932673 1-paragraph summary of 002:932671, above.

TERATOGENICITY

RAT

The upgradeable study, 017:036852, below, was originally classified as representing a "possible significant adverse effect" due to developmental effects at the highest dose (50 mg/kg/day). On reconsideration in conjunction with organizing this tox summary, it is app that the "possible adverse effect" flag should be removed: Developmental toxicity associat with marked maternal toxicity is not normally considered a primary developmental effect, a appropriately treated with much less concern than situations in which developmental toxici observed in the absence of apparent maternal toxicity (See EPA Hazard Evaluation Division Standard Evaluation Procedure: Teratology Studies [EPA-540/9-85-018]; L. D. Chitlik et al, June, 1985). (Early CDFA reviews did not necessarily consider maternal toxicity or magnit of the LEL in evaluating possible "adverse effects", however presently these factors are considered).

017 036852 Pharmaceuticals Div., Ciba-Geigy, Summit NJ, 9/18/84. Entitled: "Segment II teratology study in rats". Chlorobenzilate, tech. (not otherwise characterized). 0, 20, and 500 mg/kg/day by gavage in starch/Tween 80 suspension. Maternal toxicity NOEL = 20 mg/kg/day (salivation and lethargy down to 100 mg/kg/day). At 500 mg/kg/day, more marked clinical signs, body weight losses, and maternal mortality. Developmental toxicity NOEL = mg/kg/day (increased resorptions and delayed ossification). Not complete, not acceptable, upgradeable (needs test article characterization, analysis of dosing solutions). Original review by J. Remsen [Gee], 12/5/85, (review not on disk).
EPA 1-liner: Core Minimum, 2/17/89.

RABBIT

016 036851 Pharmaceuticals Div., Ciba-Geigy, Summit NJ, 9/18/84. Entitled: "A teratolog study of chlorobenzilate technical in New Zealand White rabbits". Chlorobenzilate, tech. otherwise characterized). 0, 5, 20, and 80 mg/kg/day by gavage in starch/Tween 80 suspens 9.

Maternal toxicity NOEL = 20 mg/kg/day (signs included decreased stools, hyperirritability)
Developmental toxicity NOEL = 80 mg/kg/day (HDT). Not complete nor acceptable, however upgradeable (needs test article characterization, analysis of dosing solutions). Original review by J. Remsen [Gee], 12/5/85, (review not on disk).
EPA 1-liner: Core Minimum, 2/17/89.

GENE MUTATION

004 042209 [See 004:932676 under DNA Damage, below, items (1) and (2).]

CHROMOSOME

No study on file.

DNA DAMAGE

004 932676 IARC, Lyon, 1974 (Appendix 38). 1-paragraph summary. Negative results repor (without data) for "(1) Back-mutation in in two strains of Serratia marcescens and forward mutation in Escherichia coli to galactose prototrophy, (2) forward mutation to streptomyci resistant E. coli, and (3) mitotic gene conversion in Saccharomyces cerevisiae.

NEUROTOXICITY

Not required at this time.